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Carvedilol Protects Better Against Vascular Events Than Metoprolol in Heart Failure

Results From COMET

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Objectives We explored whether vascular protection by carvedilol could contribute to its superior effects in the treatment of heart failure (HF) compared with metoprolol tartrate in the COMET (Carvedilol Or Metoprolol European Trial) study.

Background Full adrenergic blockade by carvedilol and additional (e.g., antioxidative) properties may lead to vascular protection relative to beta-1 blockade alone, and contribute to its efficacy in HF treatment.

Methods Three thousand twenty-nine patients with HF due to ischemic (51%) or idiopathic cardiomyopathy (44%) were randomized double-blind to carvedilol (n = 1,511) or metoprolol (n = 1,518) and followed for 58 months. Vascular end points were cardiovascular death, stroke, stroke death, myocardial infarction (MI), and unstable angina.

Results The effect of carvedilol on cardiovascular death improved consistently in subgroups with prespecified baseline variables. Myocardial infarctions were reported in 69 carvedilol and 94 metoprolol patients (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.52 to 0.97, p = 0.03). Cardiovascular death or nonfatal MI combined were reduced by 19% in carvedilol (HR 0.81, 95% CI 0.72 to 0.92, p = 0.0009 vs. metoprolol). Unstable angina was reported as an adverse event in 56 carvedilol and in 77 metoprolol patients (HR 0.71, 95% CI 0.501 to 0.998, p = 0.049). A stroke occurred in 65 carvedilol and 80 metoprolol patients (HR 0.79, 95% CI 0.57 to 1.10). Stroke or MI combined occurred in 130 carvedilol and 168 metoprolol patients (HR 0.75, 95% CI 0.60 to 0.95, p = 0.015), and fatal MI or fatal stroke occurred in 34 carvedilol and in 72 metoprolol patients (HR 0.46, 95% CI 0.31 to 0.69, p = 0.0002). Death after a nonfatal MI or stroke occurred in 61 of 124 carvedilol and in 106 of 160 metoprolol patients (HR 0.66, 95% CI 0.48 to 0.90, p = 0.0086).

Conclusions Carvedilol improves vascular outcomes better than metoprolol. These results suggest a ubiquitous protective effect of carvedilol against major vascular events. (J Am Coll Cardiol 2007;49:963–71) © 2007 by the American College of Cardiology Foundation

The benefits of beta-blockade in the treatment of heart failure (HF) are well established. In addition to angiotensin-converting enzyme (ACE) inhibitors, beta-blocking drugs improve survival and reduce cardiovascular hospitalizations, including those for worsening HF (1–4). Reverse ventricular remodeling and improved cardiac function have been

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CI = confidence interval
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NYHA = New York Heart Association

demonstrated with different types of beta-blocking drugs, and are likely to contribute to their clinical benefit (5,6). In the COMET (Carvedilol Or Metoprolol European Trial) study, carvedilol improved survival and cardiovascular hospitalizations more than the beta-1 selective beta-blocker metoprolol tartrate (7). Carvedilol blocks both the beta-1 and -2 receptor, and has tighter, more prolonged binding properties to the beta-1 receptor than metoprolol, which results in a greater sympatho-inhibitory activity than with metoprolol at the dosages used in the COMET study (8). Binding of carvedilol to the beta-2 receptor may have antiarrhythmic effects and may inhibit myocardial hypertrophy and apoptosis (9,10). Carvedilol also blocks alpha 1-adrenergic receptors with enhanced peripheral vasodilatation and renal sodium excretion (11), and has antioxidant and antiendothelin effects. These additional effects may lead to improved vascular function and vascular protection relative to the effect of beta-1 selective blockade alone. The COMET study provided a unique possibility to analyze the long-term effects on vascular-related outcomes by these agents. In this analysis, we compare the effect of carvedilol and metoprolol on vascular events in the COMET study.

Methods

The COMET study was a randomized, double-blind, parallel comparison of carvedilol, 25 mg twice a day, and metoprolol tartrate, 50 mg twice a day, in patients with stable chronic HF, New York Heart Association (NYHA) functional class II to IV and left ventricular dysfunction, in addition to standard therapy including ACE inhibition and diuretics. During an average 58-month follow-up, 1,511 patients received carvedilol and 1,518 patients metoprolol. Study design, rationale, inclusion criteria, and main results have been published (7,12). Baseline characteristics including concomitant medication were comparable between both study groups.

Eligibility criteria included stable HF, NYHA functional class II to IV, and a left ventricular ejection fraction (LVEF) ≤35%. Patients had to be on ACE inhibitor therapy for at least 4 weeks and receiving diuretics (≤40 mg furosemide or equivalent) for at least 2 weeks, and had to have been hospitalized for cardiovascular reasons at least once in the year preceding inclusion.

Patients were excluded if they had hemodynamically significant valvular disease, uncontrolled hypertension, a recent (<2 months) myocardial infarction (MI), unstable angina, coronary revascularization or stroke, an implantable cardioverter-defibrillator, or symptomatic or sustained ventricular arrhythmias despite antiarrhythmic drug therapy. Contraindication to the use of a beta-blocker, requirement of intravenous inotropic therapy, a recent change in therapy (defined as an introduction of a new therapy for HF or use of a beta- or alpha-blocking drug in the preceding 2 weeks), use of a class I antiarrhythmic agent, amiodarone >200 mg, verapamil or diltiazem, or treatment with an investigational drug 30 days before inclusion were further exclusion criteria.

Patients were assigned blindly to carvedilol, 3.125 mg twice a day (n = 1,511), or metoprolol tartrate, 5 mg twice a day (n = 1,518), at randomization. Study treatment doses were doubled every 2 weeks until the target dose of carvedilol, 25 mg twice a day, or metoprolol, 50 mg twice a day, was reached. Dosages could be adapted by the investigator at any time during the study in case of side effects. The 2 co-primary end points were: 1) all-cause mortality; and 2) all-cause mortality or all-cause hospitalization. Secondary end points included outcome variables used in this report (e.g., cardiovascular death and hospitalizations for nonfatal MI and unstable angina). An independent events committee blindly adjudicated each death first into noncardiovascular and cardiovascular deaths, and subsequently categorized the cardiovascular deaths as sudden death, death due to worsening HF, death due to stroke or other cardiovascular deaths. The latter comprised deaths due to pulmonary or mesenterial embolism or aortic dissection. The respective definitions are provided in the Appendix. Consequently, all measured outcome variables, except stroke not leading to death, were prespecified in this analysis.

Death after MI was not considered a separate mode of death, but rather an event leading to death. Myocardial infarction had to be documented in the case record form by at least 2 of 4 criteria: chest pain typical of MI for >30 min, cardiac enzymes to >2× the upper limit of normal, evolving electrocardiogram pattern suggestive of MI, or autopsy evidence of a recent MI.

For the current analysis, all MIs leading to death were grouped as fatal MI. Hospitalizations or adverse events recording an MI not leading to death were grouped as nonfatal MI.

Unstable angina pectoris was identified by the investigator as an adverse event in the case record form. Additionally, unstable angina could be identified as a cause for hospital admission or occurring during hospitalization and had to be confirmed by the absence of the aforementioned markers of MI.

All cerebrovascular accidents were defined and documented by the investigator in the case record form. The diagnosis of nonfatal stroke was provided by the investigator on the adverse event page of the case record form, whereas strokes leading to death were adjudicated as stroke death by the independent events committee.

Statistical analysis. The number of patients with any vascular event was calculated. Differences at baseline between

those who did or did not experience any vascular event were assessed using *t* tests for continuous variables and chi-square tests for categorical data.

Each of the vascular outcomes presented in this paper was calculated from the time of randomization to the time of the first event of that type. Patients who did not have an event were censored at the last study visit or at the date of death if the subject died during the study. Kaplan-Meier event rates were calculated, and differences between the treatments were assessed using Cox proportional hazard models. We used proportional hazards models with treatment as the only independent variable in the model. This is equivalent to the log-rank test and allowed us to estimate the hazard ratio (HR) and associated 95% confidence intervals (CIs). Kaplan-Meier estimates of the survivor functions were displayed to characterize the treatment effects. The end point of death after nonfatal MI or stroke is presented only for those experiencing either event. For this end point, the time to event was calculated from the time of the original event.

Results

Cardiovascular events. Cardiovascular events, including cardiovascular death, fatal or nonfatal MI, fatal or nonfatal stroke, and unstable angina, occurred in 584 patients receiving carvedilol and 667 patients receiving metoprolol (HR 0.85, 95% CI 0.76 to 0.95, p = 0.0038). Baseline characteristics of patients with or without a vascular event are compared in Table 1. Subjects experiencing an event were found to be older; had more advanced HF as shown by NYHA functional classification, duration of HF, and brain natriuretic peptide levels; a greater percentage of ischemic etiology of HF as compared with idiopathic dilated cardiomyopathy; and were more likely to have a history of MI, coronary interventions, diabetes, hypertension, and stroke. Additionally, they were treated more often with nitrates and aspirin than patients without an event.

Baseline criteria were similar in both treatment groups among those subjects with an event, apart from a slight difference in the initial NYHA functional classification (NYHA II/III/IV, carvedilol 36%/59%/5%, metoprolol 39%/53%/8%, p = 0.0358).

Cardiovascular mortality. Cardiovascular deaths occurred in 438 (29%) patients receiving carvedilol and in 534 (35%) patients in the metoprolol group (HR 0.80, 95% CI 0.70 to 0.90, p = 0.0004). Baseline characteristics were examined, but no differences were found between the treatment groups (data not shown).

The superior effect of carvedilol on cardiovascular death was consistent in subgroups with pre-specified baseline variables, such as gender, age (≤ or >65 years), NYHA functional classification, LVEF ≤ or >25%, heart rate ≤ or >80 beats/min, history of ischemic heart disease, previous MI, diabetes, angina, hypertension, atrial fibrillation, and receiving antiplatelet or anticoagulant therapy (Fig. 1).

MI. A fatal MI occurred in 21 carvedilol and in 36 metoprolol patients (HR 0.57, 95% CI 0.33 to 0.98, p = 0.041) (Fig. 2). This different effect of carvedilol on fatal MI started relatively early, during the first year of treatment (Fig. 3).

When fatal and nonfatal MIs were combined, carvedilol significantly reduced the occurrence of all MIs by 29% (HR 0.71, 95% CI 0.52 to 0.97, p = 0.033) (Fig. 2).

Unstable angina. Unstable angina was reported as an adverse event in 56 carvedilol patients and in 77 patients receiving metoprolol (HR 0.71, 95% CI 0.501 to 0.998, p = 0.049) (Fig. 2). Hospitalizations for unstable angina were reduced by 17% by carvedilol (HR 0.83, 95% CI 0.64 to 1.09, p = 0.185).

Stroke. A stroke was reported in 65 patients in the carvedilol group and in 80 patients treated with metoprolol (HR 0.79, 95% CI 0.57 to 1.10, p = 0.163) (Fig. 2). Baseline criteria were comparable in both groups with the exception of patients in the metoprolol group being older than carvedilol patients (68 ± 9.0 years vs. 65 ± 8.3 years, respectively, mean ± SD, p = 0.0075). Fatal strokes occurred in 13 carvedilol versus 38 metoprolol patients (HR 0.33, 95% CI 0.18 to 0.62, p = 0.0006) (Fig. 2).

Effect of carvedilol on combined vascular events. The effect of carvedilol on the combined end point of MI or stroke was significant (HR 0.75, 95% CI 0.60 to 0.95, p = 0.015), and the effect on fatal MI or fatal stroke was highly significant (HR 0.46, 95% CI 0.31 to 0.69, p = 0.0002). Effect differences started early during the first year of treatment and remained constant over time (Fig. 3).

Carvedilol reduced the risk of any MI, any unstable angina, or any stroke by 19% (p = 0.017) (Figs. 2 and 4).

The occurrence of cardiovascular death and nonfatal MI was significantly reduced by carvedilol (HR 0.81, 95% CI 0.72 to 0.92, p = 0.0009) as was the combination of all-cause mortality and nonfatal MI (HR 0.84, 95% CI 0.75 to 0.94, p = 0.0026) (both Fig. 2). Also, cardiovascular death, nonfatal MI, or stroke was reduced (HR 0.83, 95% CI 0.74 to 0.94, p = 0.0022). Again, changes occurred early, and the difference in effect remained constant during the study (Fig. 5).

The occurrences of cardiovascular death and unstable angina or stroke, respectively, were significantly reduced in favor of carvedilol, as were the combinations of all-cause death and unstable angina and all-cause death and stroke (Fig. 2).

Mortality after stroke/MI. Death after nonfatal MI or nonfatal stroke occurred in 61 of 124 patients on carvedilol and 106 or the 160 patients on metoprolol. This was a significant treatment difference (HR 0.66, 95% CI 0.48 to 0.90, p = 0.0086) (Fig. 6).

Treatment effect on vascular end points in patients with or without a history of ischemic heart disease. The effect of carvedilol was comparable in both patients with a history of ischemic heart disease and in those without such a history, albeit that the effect of carvedilol was more robust

Table 1 Baseline Characteristics of Patients With or Without a Cardiovascular End Point (Fatal or Nonfatal MI/Fatal or Nonfatal Stroke/Unstable Angina/Cardiovascular Death)

	Any Event (n = 1,251)	No Event (n = 1,778)	Total (n = 3,029)	p Value
Age (yrs), mean/SD	64.9/10.5	59.9/11.5	62.0/11.4	<0.0001
Gender (% male)	80.5	79.3	79.8	0.4207
Body mass index (kg/m^2), mean/SD	26.4/4.3	27.2/4.5	26.9/4.4	<0.0001
Systolic BP (mm Hg), mean/SD	123.8/20.1	127.7/18.9	126.1/19.5	<0.0001
Diastolic BP (mm Hg), mean/SD	75.5/11.1	78.3/10.6	77.1/10.9	<0.0001
Heart rate (beats/min), mean/SD	80.8/13.2	81.3/13.4	81.1/13.4	0.2668
NYHA functional class, %				
II	37.7	55.9	48.4	<0.0001
III	56.0	42.1	47.8	
IV	6.3	2.0	3.8	
Duration CHF (months) mean/median	51.8/31.0	35.7/15.0	42.4/21.0	<0.0001
Etiology CHF,* %				
Ischemic heart disease	66.1	43.0	52.5	<0.0001
Hypertension	18.9	16.9	17.7	0.1415
Dilated cardiomyopathy	31.4	52.7	43.9	<0.0001
LVEF mean/SD	25.4/7.2	26.6/7.1	26.1/7.2	<0.0001
NT-proBNP (pg/ml) median	1,871	970.6	1,242	<0.0001
Previous MI, %	53.5	33.1	41.5	<0.0001
Current angina, %	27.9	17.2	21.6	<0.0001
Previous angioplasty, %	9.9	6.9	8.1	0.0024
Previous CABG, %	22.2	13.4	17.0	<0.0001
Hypertension, %	39.3	35.2	36.9	0.0201
Diabetes, %	28.9	20.8	24.2	<0.0001
Stroke, %	8.9	5.8	7.1	0.0011
Concomitant medication at randomization, %				
Diuretics*	98.9	98.6	98.7	0.4903
ACE inhibitors*	90.8	91.7	91.4	0.3726
Angiotensin receptor antagonists	6.4	6.6	6.5	0.7909
Digitalis	61.3	58.1	59.4	0.0763
Antiarrhythmics	14.8	10.3	12.1	0.0002
Nitrates	43.0	25.5	32.8	<0.0001
Aldosterone antagonists	12.7	9.4	10.8	0.0044
Beta-blockers†	5.0	3.8	4.3	0.1303
Anticoagulants	45.8	45.7	45.7	0.9419
Aspirin	42.4	32.9	36.8	<0.0001
Lipid-lowering agents (statins)	20.9	21.3	21.1	0.7923
Laboratory measurements				
Hemoglobin level (g/dl)	14.0/1.6	14.3/1.5	14.2/1.5	<0.0001
Serum creatinine (μmol/l)	115.5/48.8	101.4/33.5	107.2/41.1	<0.0001
Blood glucose (mmol/l)	6.9/3.2	6.4/2.7	6.6/2.9	<0.0001

*Inclusion criteria; †stopped before study start.

ACE = angiotensin-converting enzyme; BP = blood pressure; BNP = brain natriuretic peptide; CABG = coronary bypass surgery; CHF = chronic heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

on some end points (e.g., fatal MI in patients with a history of ischemic heart disease). However, interaction tests did not show a significant difference in study treatment effect between the 2 groups for any of the end points. These data are presented in Table 2.

Discussion

This analysis indicates a consistently greater effect on major cardiovascular events, including MI, unstable angina, stroke, and cardiovascular death, by carvedilol as compared with metoprolol tartrate. With the exception of hospitalization for unstable angina and any strokes, all parameters measured were significantly reduced by carvedilol. These results strongly suggest a protective effect of carvedilol against major vascular events.

As previous analyses have also indicated that carvedilol reduces the occurrence of sudden death and death due to worsening HF (7), a decrease in ischemic events may well contribute to this survival benefit, in addition to other mechanisms including hemodynamic improvement and antiarrhythmic properties of carvedilol (9,13–17).

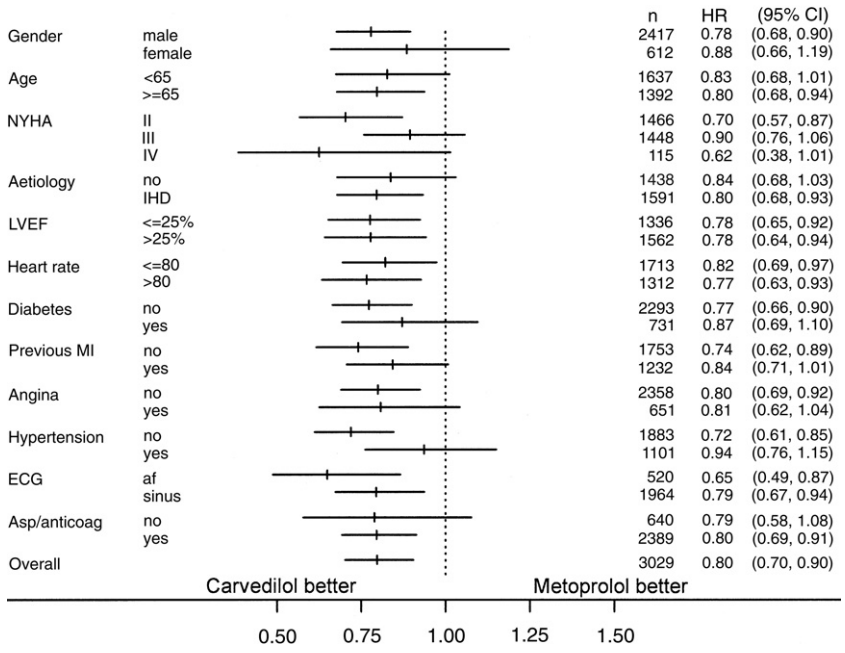

Figure 1 **Risk of Cardiovascular Death by Subgroups With Predefined Baseline Variables**

Carvedilol consistently improves cardiovascular death compared with metoprolol. af = atrial fibrillation; Asp/anticoag = aspirin/anticoagulant; CI = confidence interval; ECG = electrocardiogram; HR = hazard ratio; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association functional classification.

The vascular protective effect of carvedilol is probably dependent on different mechanisms, and the result of its complex pharmacologic profile.

The vascular endothelium contains both beta-1 and -2 as well as alpha-1 receptors. Blockade of all 3 adrenergic receptors by carvedilol provides for better endothelium-

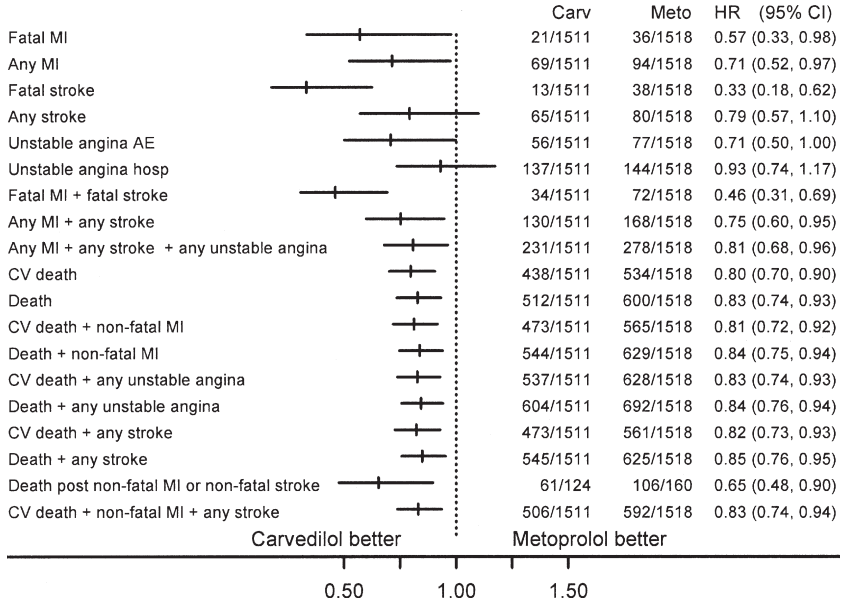

Figure 2 **Effect of Carvedilol Compared With Metoprolol on Single and Combined Vascular Events**

With few exceptions, carvedilol (Carv) consistently reduces vascular event risk. AE = adverse event; CV = cardiovascular; hosp = hospitalization; Meto = metoprolol; other abbreviations as in Figure 1.

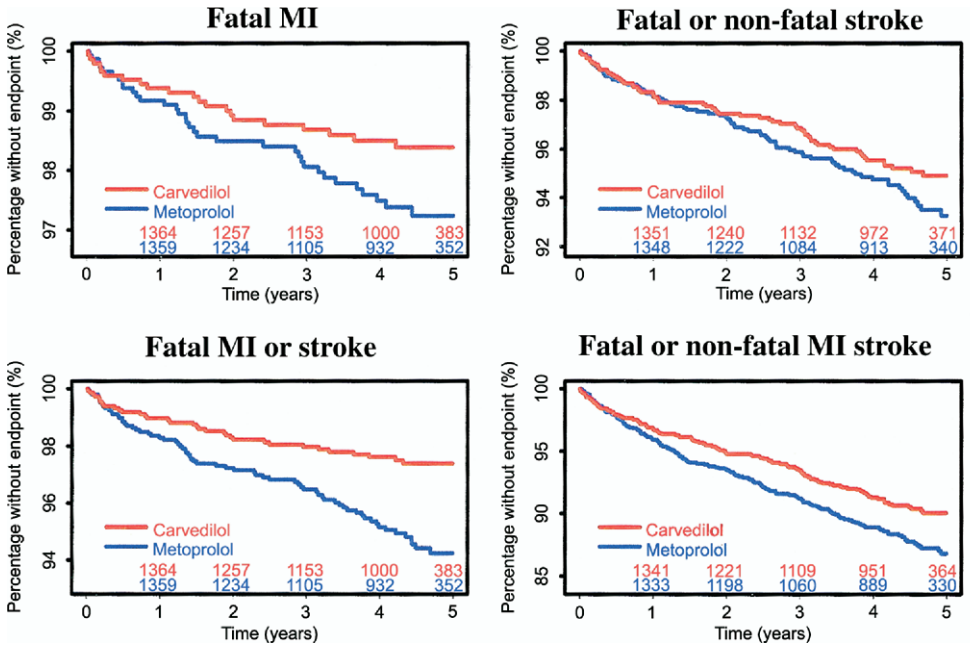

Figure 3 **Kaplan-Meier Plots of Time to Fatal MI, Any Stroke, Fatal MI or Stroke, and Any MI or Stroke in the 2 Treatment Groups**

There were significantly fewer events in the carvedilol group than in the metoprolol group for all these end points barring any stroke. The effect of carvedilol started early and was constant over time. MI = myocardial infarction.

dependent vasodilatation than more selective beta-blockade (18). Both in animal and human studies, carvedilol, but not metoprolol, results in vasodilatation and better improves endothelial function (19,20). Also, antioxidative and anti-apoptotic properties of carvedilol may play a role in improving free radical-induced endothelial dysfunction, reduce myocardial injury and infarct size after ischemia-reperfusion, and may affect atherosclerosis formation (21–30). Moreover, carvedilol, but not beta-1 adrenergic blockade, suppresses norepinephrine release from the ischemic heart, which is likely to contribute to better anti-ischemic effects, vaso-dynamics, and, possibly, vasculo-protection by the drug (31).

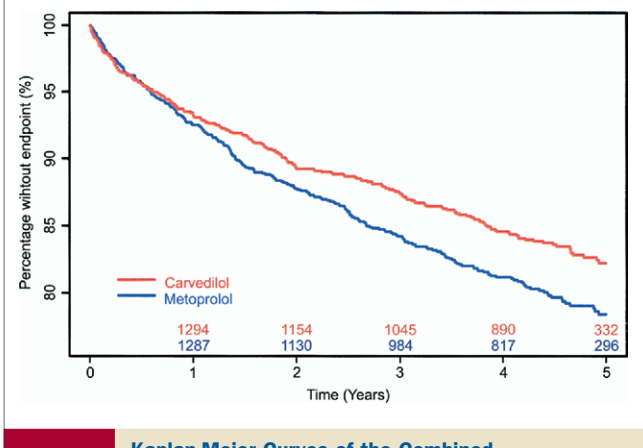

Figure 4 **Kaplan-Meier Curves of the Combined End Point of any MI, Unstable Angina, and Stroke**

Significant greater reduction of the combined end point of any myocardial infarction (MI), unstable angina, and stroke with carvedilol than with metoprolol.

Taken together, the vascular protective and anti-ischemic effects observed with carvedilol are likely to contribute to the clinical benefit of the drug in the COMET study, in relation to the effect of metoprolol. Death in patients with HF is often linked to an acute ischemic event. Although this is obviously the case for MI and stroke deaths, sudden death is also frequently the result of an acute coronary ischemic event. Indeed, in the COMET study, carvedilol significantly reduced sudden death to a larger extent than metoprolol (7).

It has been hypothesized before that that the beneficial effects of carvedilol, compared with metoprolol tartrate, may be partially explained by a greater degree of blockade of the beta-1 adrenergic receptors. The greater effect of carvedilol on heart rate, compared with metoprolol, has been used to support this hypothesis. However, this difference was minimal (−1.6 beats/min with carvedilol compared with metoprolol) and significant only at 4, 8, and 16 months (7).

Moreover, in a post-hoc analysis of our data, the effects of carvedilol, compared with metoprolol, on outcome were independent of any change in heart rate, and no interaction with heart rate, systolic blood pressure, or the beta-blocker dose was found (32).

We, therefore, consider the vascular effects of carvedilol the result of its specific pharmacologic profile, and not the result of more intense beta-1 blockade than metoprolol in our study.

Carvedilol's vasculo-protective and anti-ischemic properties are likely to contribute to a greater improvement in cardiac function in HF than beta-1–selective blocking agents. Several smaller studies and a recent meta-analysis indicate that long-term treatment with carvedilol results in a greater increase in LVEF than metoprolol (13–16).

In the CHRISTMAS (Carvedilol Hibernating Reversible ISchaemia Trial: MArker of Success) study, improvement of left ventricular function with carvedilol in patients with HF of ischemic origin was greater if more myocardium was affected by hibernation or ischemia was present (33). This supports the suggestion that the beneficial effect of carvedilol in the COMET study may partly be due to its anti-ischemic properties. The results of the COMET study may have a wider application than just to patients with HF. Carvedilol may well be considered the drug of choice in other conditions likely to result in or be aggravated by myocardial ischemic events, whenever the use of beta-blockade is considered.

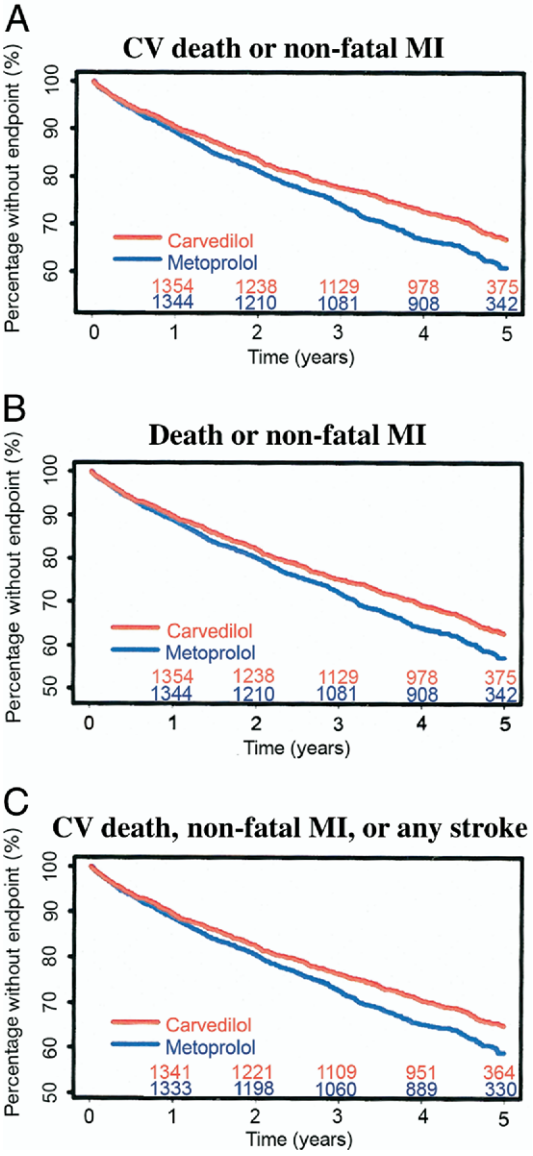

Figure 5 **Time to CV Death or Nonfatal MI, Death or Nonfatal MI, CV Death, Nonfatal MI, or Any Stroke**

Kaplan-Meier curves for the combined end point of cardiovascular (CV) death or nonfatal myocardial infarction (MI) **(A)**, all-cause death or nonfatal MI **(B)**, and CV death, nonfatal MI, or any stroke **(C)**.

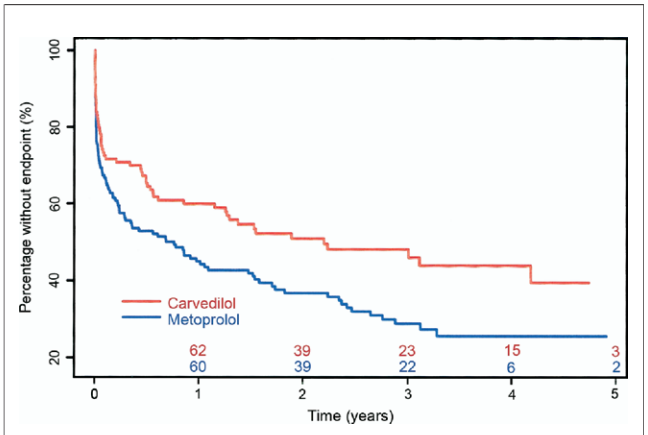

Figure 6 **Kaplan-Meier Curves for Death After a Nonfatal Myocardial Infarction or Nonfatal Stroke**

Carvedilol significantly reduces death after a nonfatal myocardial infarction or stroke compared with metoprolol.

Study limitations. Whereas all fatal events were adjudicated by the events committee in the COMET study, nonfatal events were not. These were classified in a blinded fashion either from the hospitalization reports or from the adverse events pages of the case record form if the event had not led to hospitalization in the investigator's own clinic. Events were only collected for further analysis if a clear description was available. However, any hospitalization at the investigator's site for an acute MI had to be confirmed by predefined ECG and enzymatic criteria, and for unstable angina by the absence of these criteria. By doing so, we tried to limit misclassification of nonfatal events as much as possible, and this likely contributed to the consistency and comparable magnitude of treatment effect of carvedilol on the different fatal and nonfatal vascular events.

Conclusions

This present analysis of the COMET study indicates that carvedilol reduces vascular events, whether fatal or not, to a greater extent than metoprolol tartrate. The anti-ischemic properties of carvedilol can be explained by several mechanisms contributing to vasculo-protection by the drug. These effects are clinically relevant, and likely to contribute to the superior therapeutic profile of this beta-blocker in the treatment of HF.

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Table 2 Events in IHD and Non-IHD Subgroups and Interaction Between Study Medication and Subgroups

	Events		Carvedilol vs. Metoprolol		
	Carvedilol	Metoprolol	HR (95% CI)	p Value	Interaction p Value
Fatal MI					
IHD	17/776 (2.2%)	32/815 (3.9%)	0.55 (0.31–1.00)	0.048	0.509
No IHD	4/735 (0.5%)	4/703 (0.6%)	0.92 (0.23–3.66)	0.900	
Any MI					
IHD	58/776 (7.5%)	77/815 (9.4%)	0.78 (0.56–1.10)	0.155	0.511
No IHD	11/735 (1.5%)	17/703 (2.4%)	0.59 (0.28–1.25)	0.169	
Fatal stroke					
IHD	10/776 (1.3%)	23/815 (2.8%)	0.45 (0.21–0.95)	0.035	0.226
No IHD	3/735 (0.4%)	15/703 (2.1%)	0.18 (0.05–0.64)	0.007	
Any stroke					
IHD	42/776 (5.4%)	53/815 (6.5%)	0.82 (0.55–1.23)	0.329	0.901
No IHD	23/735 (3.1%)	27/703 (3.8%)	0.79 (0.45–1.37)	0.397	
Unstable angina AE					
IHD	49/776 (6.3%)	65/815 (8.0%)	0.78 (0.54–1.14)	0.197	0.458
No IHD	7/735 (1.0%)	12/703 (1.7%)	0.53 (0.21–1.34)	0.179	
Unstable angina hospitalization					
IHD	109/776 (14.0%)	122/815 (15.0%)	0.92 (0.71–1.19)	0.540	0.443
No IHD	28/735 (3.8%)	22/703 (3.1%)	1.18 (0.67–2.06)	0.567	
Fatal MI + fatal stroke					
IHD	27/776 (3.5%)	53/815 (6.5%)	0.53 (0.33–0.84)	0.007	0.374
No IHD	7/735 (1.0%)	19/703 (2.7%)	0.34 (0.14–0.81)	0.014	
Any MI + any stroke					
IHD	96/776 (12.4%)	124/815 (15.2%)	0.80 (0.61–1.04)	0.099	0.652
No IHD	34/735 (4.6%)	44/703 (6.3%)	0.71 (0.45–1.11)	0.133	
Any MI + any stroke + any unstable angina					
IHD	174/776 (22.4%)	218/815 (26.7%)	0.82 (0.67–1.00)	0.051	0.753
No IHD	57/735 (7.8%)	60/703 (8.5%)	0.88 (0.61–1.26)	0.475	
CV death					
IHD	268/776 (34.5%)	348/815 (42.7%)	0.80 (0.68–0.93)	0.005	0.705
No IHD	170/735 (23.1%)	186/703 (26.5%)	0.84 (0.68–1.03)	0.093	
Death					
IHD	314/776 (40.5%)	381/815 (46.7%)	0.85 (0.73–0.99)	0.033	0.827
No IHD	198/735 (26.9%)	219/703 (31.2%)	0.83 (0.68–1.00)	0.052	
CV death + non-fatal MI					
IHD	297/776 (38.3%)	372/815 (45.6%)	0.82 (0.71–0.96)	0.013	0.928
No IHD	176/735 (23.9%)	193/703 (27.5%)	0.83 (0.68–1.02)	0.082	
Death + non-fatal MI					
IHD	340/776 (43.8%)	403/815 (49.4%)	0.87 (0.75–1.00)	0.058	0.665
No IHD	204/735 (27.8%)	226/703 (32.1%)	0.82 (0.68–1.00)	0.046	
CV death + any unstable angina					
IHD	346/776 (44.6%)	427/815 (52.4%)	0.83 (0.72–0.96)	0.009	0.660
No IHD	191/735 (26.0%)	201/703 (28.6%)	0.87 (0.72–1.07)	0.183	
Death + any unstable angina					
IHD	389/776 (50.1%)	458/815 (56.2%)	0.87 (0.76–0.99)	0.038	0.835
No IHD	215/735 (29.3%)	234/703 (33.3%)	0.84 (0.70–1.02)	0.073	
CV death + any stroke					
IHD	287/776 (37.0%)	366/815 (44.9%)	0.81 (0.69–0.95)	0.008	0.535
No IHD	186/735 (25.3%)	195/703 (27.7%)	0.88 (0.72–1.08)	0.209	
Death + any stroke					
IHD	332/776 (42.8%)	397/815 (48.7%)	0.86 (0.75–1.00)	0.048	0.972
No IHD	213/735 (29.0%)	228/703 (32.4%)	0.86 (0.71–1.04)	0.113	
Death post-non-fatal MI or non-fatal stroke					
IHD	48/90 (53.3%)	79/117 (67.5%)	0.73 (0.51–1.05)	0.092	0.209
No IHD	13/34 (38.2%)	27/43 (62.8%)	0.48 (0.25–0.94)	0.033	
CV death + non-fatal MI + any stroke					
IHD	314/776 (40.5%)	390/815 (47.9%)	0.83 (0.72–0.96)	0.014	0.681
No IHD	192/735 (26.1%)	202/703 (28.7%)	0.87 (0.72–1.06)	0.182	

AE = adverse event; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction.

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APPENDIX

For definitions of the modes of death, please see the online version of this article.